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(29) Inhibiting delta 5-desaturase and conversion of dihomogamma-linolenic acid to arachidonic acid.

(30) A composition for inhibiting  $\Delta^5$ -desaturase comprising an effective ingredient selected from the group consisting of lignan compounds, curcumin and piperonyl butoxide. As the lignan compounds sesamin, sesaminol, episesamin, episesaminol, sesamol, 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane, 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenoxy)-3,7-dioxabicyclo[3.3.0]octane, and 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenoxy)-3,7-dioxabicyclo[3.3.0]octane are used. Moreover the effective ingredient may be a sesame oil extract or sesame seed extract.

EP 0 387 000 A2

# INHIBITING $\Delta^5$ -DESATURASE AND CONVERSION OF DIHOMO- $\gamma$ -LINOLENIC ACID TO ARACHIDONIC ACID

The present invention provides an inhibitor for  $\Delta^5$ -desaturase which specifically inhibits a conversion of dihomomethylolonic acid to arachidonic acid. This inhibitor remarkably increases, in vivo, an amount of dihomomethylolonic acid in comparison with arachidonic acid.

Various studies relating to the actions of essential fatty acids on an organism show that not only there are two metabolic pathways for essential fatty acids, which pathways strongly influence each other, but also in the same metabolic pathway there are various metabolites which act antagonistically, and therefore, to enhance an action it is necessary not only to administer a related metabolite but also to inhibit an antagonistic action against the above-mentioned action. In the case of dihomomethylolonic acid and a metabolite thereof, i.e., arachidonic acid, an eicosanoid derived from dihomomethylolonic acid and an eicosanoid derived from arachidonic acid antagonistically influence each other, and therefore, to enhance the effects of an administration of dihomomethylolonic acid, it is necessary to inhibit a conversion of dihomomethylolonic acid to arachidonic acid. At present, although a series of prostaglandin 1 derived from dihomomethylolonic acid is known to have an antithrombus activity, unless inhibiting the conversion of dihomomethylolonic acid to arachidonic, the desired expected effect provided by administering dihomomethylolonic acid is not obtained.

It is known that among lignan compounds, sesaminol, episesaminol, 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane, 2,6-bis-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane and 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane are comparable with or superior to sesaminol and  $\gamma$ -tocopherol in the antioxidant activity thereof, and are being developed as antioxidants. Moreover, these lignan compounds are under study for possible application for an inhibition of lipid peroxidation in vivo which is considered a cause of senility, oncogenesis and the like. However, among lignan compounds, an anti-oxidation activity of sesamin, episesamin and sesaminol is not known.

Moreover, it is not known that the above-mentioned lignan compounds inhibit  $\Delta^5$ -desaturase, which catalyzes the conversion of dihomomethylolonic acid to arachidonic acid.

In addition, it is not known that curcumin and piperonyl inhibit  $\Delta^5$ -desaturase.

Accordingly, the present invention provides a composition for an inhibition of  $\Delta^5$ -desaturase, comprising a compound selected from the group consisting of lignan compounds, curcumin and piperonyl butoxide.

In another aspect, these compounds are provided for the medical use.

Fig. 1 is a graph showing that sesamin specifically inhibits  $\Delta^5$ -desaturase;

Fig. 2 is a graph showing that episesamin specifically inhibits  $\Delta^5$ -desaturase; and

Fig. 3 is a graph showing that sesaminol specifically inhibits  $\Delta^5$ -desaturase.

The present inventors found that lignan compounds, which inhibit  $\Delta^5$ -desaturase in a biosynthesis pathway for highly unsaturated fatty acids in arachidonic acid-producing microorganisms, also inhibit  $\Delta^5$ -desaturase in an enzyme cascade in rat liver microsome.

This inhibitory activity is provided by lignans such as sesamin, sesaminol, episesamin, episesaminol, sesaminol, 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane, 2,6-bis-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane and 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane; curcumin of plant origin; as well as piperonyl butoxide which is a synergistic agent for agricultural chemicals.

The inhibition of the  $\Delta^5$ -desaturase increases a level of dihomomethylolonic acid in vivo, which in turn increases levels of prostaglandin 1 series compounds through the enhancement of dihomomethylolonic acid cascade. Namely, the increase of the dihomomethylolonic acid level leads to an increase of the eicosanoid thereof, i.e., prostaglandin G<sub>1</sub> (PGG<sub>1</sub>); prostaglandin H<sub>1</sub> (PGH<sub>1</sub>); prostaglandin D<sub>1</sub> (PGD<sub>1</sub>); prostaglandin E<sub>1</sub> (PGE<sub>1</sub>); prostaglandin F<sub>1 $\alpha$</sub>  (PGF<sub>1 $\alpha$</sub> ); thromboxane A<sub>1</sub> (TXA<sub>1</sub>); thromboxane B<sub>1</sub> (TXB<sub>1</sub>); 12-(S)-hydroxy-8,10,14-eicosatrienoic acid (12-HPETRE); 11-hydroperoxy-8,12,14-eicosatrienoic acid (11-HPETRE); 12-hydroperoxy-pentadecadienoic acid (HHD); 11-hydroperoxy-8,12,14-eicosatrienoic acid (11-HPETRE); 12-hydroperoxy-8,12,14-eicosatrienoic acid (12-HPETRE); 15-hydroperoxy-8,11,13-eicosatrienoic acid (15-HPETRE); 11-hydroxy-8,11,13-eicosatrienoic acid (11-HETRE); 12-hydroxy-8,10,14-eicosatrienoic acid (12-HETRE); 15-hydroxy-8,11,13-eicosatrienoic acid (15-HETRE); 8-hydroperoxy-9,11,14-eicosatrienoic acid (8-HPETRE); 8-hydroxy-9,11,14-eicosatrienoic acid (8-HETRE); 8,9-leukotriene A<sub>3</sub> (8,9-LTA<sub>3</sub>); 8,15-leukotriene B<sub>3</sub> (8,15-LTB<sub>3</sub>); 8,9-leukotriene C<sub>3</sub> (8,9-LTC<sub>3</sub>); 8,9-leukotriene D<sub>3</sub> (8,9-LTD<sub>3</sub>); 8,9-leukotriene E<sub>3</sub> (8,9-LTE<sub>3</sub>); 8,9-leukotriene F<sub>3</sub> (8,9-LTF<sub>3</sub>), and the like.

These derived compounds provide advantageous activities. For example, it is known that PGE<sub>1</sub> exhibits anti-platelet aggregation activity, vasodilatation activity, bronchodilatation activity, and antiinflammation

activity, and are being studied for clinical application to treatment of pulmonary trunk thrombosis, and thromboembolism, pulmonary hypertension, bronchial asthma, congestive heart, new born blue disease, and skin diseases. Moreover, the compounds overcome the disadvantages that PGE<sub>1</sub>, which having very strong biological activities, can be only partially absorbed as an active form in an oral administration of native prostaglandin (PG). This drawback is caused by an inactivation of PG at the wall of gastro-intestinal tract, and therefore, it has been considered that the development of a stable PG derivative or an injection of PG is necessary. Nevertheless, use of inhibitor for  $\Delta^5$ -desaturase may regulate a fatty acid biosynthesis *in vivo*, and provides various pharmacological activities, such as anti-inflammation activity, anti-thrombus activity, blood pressure-lowering activity and the like through increasing levels of dihomom- $\gamma$ -linolenic acid and eicosanoids thereof.

Moreover, the above-mentioned active compounds are promising as functional factors for functional foods. Since the lignan compounds having an activity of inhibiting  $\Delta^5$ -desaturase are those inherently contained in edible oils, then are safe as functional factors for functional foods.

Lignan compounds as enzyme inhibitors of the present invention can be prepared, for example, as follows. First, an extract containing the lignans is obtained from sesame oil. The sesame oil may be purified with sesame oil or crude sesame oil prior to a decoloring step. To obtain the extract, sesame oil is extracted with an organic solvent which is substantially immiscible with the sesame oil and can extract and dissolve effective ingredients. The organic solvents are, for example, acetone, methyl ethyl ketone, diethyl ketone, methanol, ethanol, and the like. To extract the effective ingredients, for example, sesame oil and the solvent are homogeneously mixed, and the mixture is allowed to stand at a low temperature, for example, -80° C. Phases are separated by a conventional procedure such as centrifugation to obtain an organic phase, which is then evaporated to obtain an extract. Next, individual compounds can be isolated from the extract. To this end, the extract can be separated by a conventional procedure, such as column chromatography, high performance liquid chromatography, distillation, crystallization, or a combination thereof. More specifically, the extract is subjected to high performance liquid chromatography using a reverse column (5C<sub>18</sub>) and an eluate, i.e., methanol/water (60:40) to obtain fractions containing desired lignans. After distilling off the solvent a crystal is obtained which is then recrystallized from ethanol. In this manner, sesamin, episesamin, sesaminol and episesaminol are obtained from purified sesame oil.

Alternatively, an extract useful for the present invention can be obtained from sesame seeds. In this case, sesame seeds, if necessary after grinding, are extracted with any solvent able to extract the sesame oil, for example, an organic solvent described above. After separating the solvent from the residue, the solvent is evaporated to obtain an extract. An extract obtained from crude sesame oil, or sesame seeds contains lignans such as sesamin, sesaminol, episesamin, episesaminol, sesaminol, 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane, 2,6-bis-(3-methoxy-4-hydroxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane and 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenoxy)-3,7-dioxabicyclo[3.3.0]octane. These lignans can be isolated as described above.

Note, the above-mentioned processes for the isolation of lignans are examples only, and this can be obtained with other processes.

Moreover, the present enzyme inhibitors can be used as a form of derivative of glycoside or the like, so far as the enzyme inhibitory activity is maintained.

The  $\Delta^5$ -desaturase inhibitor can be used to increase an *in vivo* level of dihomom- $\gamma$ -linolenic acid, and to enhance the dihomom- $\gamma$ -linolenic acid cascade, resulting in an increase of the levels of prostaglandin 1 series compounds. On the basis of these properties, the present enzyme inhibitors are promising as medicaments for anti-inflammation, antithrombus, blood pressure lowering activities and the like.

The lignan compounds, piperonyl butoxide, or curcumin used as active ingredient in the present enzyme inhibitory composition can be used alone, or in an appropriate combination. These compounds are dissolved in ethanol, and the resulting solution diluted with water before use. Alternatively, the compounds may be formulated as an emulsion in an aqueous solution, or in capsules. Moreover, the present active ingredient can be converted to inclusion bodies with cyclodextrin, which are then formulated to powders, particles, tablets, and other conventional formulations.

The present enzyme inhibitors can be also used in combination with other materials, such as sugars, lipids, proteins or the like, to enhance the effects of the enzyme inhibitors as functional factors. Further, to enhance the effects of the enzyme inhibitors, they may be used in combination with a lipid, for example, a fatty acid having 2 to 20 carbon atoms, such as acetic acid, propionic acid, butyric acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, myristoleic acid, stearic acid, oleic acid, linoleic acid, arachidic acid, eicosenoic acid, eicosadienoic acid, dihomom- $\gamma$ -linolenic acid or the like, alone or in the form of salt such as sodium salt, potassium salt or ammonium salt, ester such as methyl ester or ethyl ester. Moreover, oils containing such fatty acids, for example, conventional oils such as camellia oil,

castor oil, chlorophyll oil, corn oil, cottonseed oil, croton oil, linseed oil, olive oil, peanut oil, rapeseed oil, sesame oil, soybean oil, tung oil, whale oil, and coconut oil can be used.

## 5 Examples

The present invention will now be further illustrated by, but is no means limited to, the following examples.

### 10 Example 1

As a homogenization solution, a 50 mM phosphate buffer (pH 7.4) containing 0.15M KCl, 5 mM  $MgCl_2 \cdot 6H_2O$ , 1 mM EDTA, 0.25M saccharose and 1.5 mM glutathione was used. The liver of a Wister male rat was perfused with physiological saline and removed, and to the removed liver was added 4-fold by weight of the homogenization solution, and the whole was homogenized. The homogenate was centrifuged at 10,000 xg for 20 minutes to obtain a supernatant, which was centrifuged at 100,000 xg for one hour to obtain a pellet. The pellet was suspended in the homogenization solution to obtain a microsome solution containing 12.24 mg/ml protein. The above-mentioned procedures were carried out at 4°C.

To assay the  $\Delta^5$ -desaturase activity, 100  $\mu$ l of the rat liver microsome solution was added to 1 ml of 0.1M phosphate buffer (pH 7.4) containing 0.25M saccharose, 0.15M KCl, 1.5 mM glutathione, 45 mM NaF, 0.5 mM nicotinamide, 5 mM  $MgCl_2 \cdot 6H_2O$ , 7.5 mM ATP, 0.4 mM  $COA \cdot Na_2$ , 1.5 mM NADH, and 100  $\mu$ M dihomono- $\gamma$ -linolenic acid containing 0.1  $\mu$ Ci (1.7 nmoles) [ $2^{14}C$ ]-dihomo- $\gamma$ -linolenic acid per 1 ml, the mixture was incubated at 37°C for one hour, followed by an addition of 5 ml of ethanol to terminate the reaction. To the reaction mixture was added 1 ml of 4N KOH, and mixture was incubated at 60°C for 30 minutes for saponification. After the reaction, 3 ml of water, 100  $\mu$ g of dihomono- $\gamma$ -linolenic acid and 1 ml of 6N HCl were added thereon, and fatty acids in the reaction mixture were extracted twice with 5 ml of hexane. The extract was evaporated in a centrifuge evaporator and 1 ml of ethyl ether:methanol (9:1) was added to the residue, and the fatty acids were methylated with diazomethane. After allowing to stand at room temperature for 30 minutes, the reaction mixture was evaporated in a centrifuge evaporator to remove the solvent, whereby methyl esters of the resulting fatty acids were obtained. The esters were separated on a 10%  $AgNO_3$  silica gel plate using petroleum ether/ethyl ether (1:1) as a developing solvent. Silica gel portions corresponding to the substrate dihomono- $\gamma$ -linolenic acid and the product arachidonic acid respectively were peeled off, and to 5 ml of toluene-based scintillation fluid solution was added to the silica gel to measure the radioactivity by a scintillation counter. The radioactivity of the generated arachidonic acid was determined by subtracting a radioactivity at the onset of the reaction from a radioactivity after the reaction.

The enzyme inhibitory activities of sesamin, episesamin and sesamol were measured according to the above-mentioned procedure, except that the reaction mixture contained 0.001 to 0.5 mg/ml sesamin, episesamin or sesamol. The radioactivity was measured as described above, and the percent inhibition was calculated.

For the assay of  $\Delta^6$ -desaturase and  $\Delta^5$ -desaturase, substantially the same procedure as described above was repeated, except that 100 nmoles of linoleic acid including 0.1  $\mu$ Ci (1.70 nmoles) of [ $1^{14}C$ ]-linoleic acid, and 100 nmoles of stearic acid including 0.1  $\mu$ Ci (1.79 nmoles) of [ $1^{14}C$ ]-stearic acid were used as substrates respectively; and petroleum ether/ethyl ether (7:3) and petroleum ether:ethyl ether (95:5) were used respectively to separate the substrate and product in the thin layer chromatography step. The inhibitory action of sesamin, episesamin and sesamol on  $\Delta^6$ -desaturase and  $\Delta^5$ -desaturase was measured as above.

The inhibitory action of sesamin on  $\Delta^5$ -desaturase,  $\Delta^6$ -desaturase and  $\Delta^3$ -desaturase is shown in Fig. 1 and the inhibitory action of episesamin and sesamol on  $\Delta^5$ -desaturase and  $\Delta^6$ -desaturase is shown in Figs. 2 and 3. As seen from Figs. 1, 2 and 3, sesamin, episesamin and sesamol inhibited the  $\Delta^5$ -desaturation reaction from dihomono- $\gamma$ -linolenic acid to arachidonic acid.

From this result, it is clear that sesamin, episesamin and sesamol inhibit  $\Delta^5$ -desaturase occurring in animals, which inhibit the conversion of dihomono- $\gamma$ -linolenic acid to arachidonic acid. Moreover, in addition to sesamin, episesamin and sesamol, it is believed that other lignan compounds can be used, for example, an extract prepared from sesame oil by organic solvent extraction and a component therein such as sesamol [2-(3,4-methylenedioxy-6-hydroxyphenyl)-6-(3,4-methylenedioxyphenyl)-cis-dioxabicyclo[3.3.0]-sesaminol] as well as an extract from sesame seeds by acetone and a component therein, such as 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane, 2,6-bis-(3-

methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3,3,0]octane and 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenoxy)-3,7-dioxabicyclo[3,3,0]octane specifically inhibit  $\Delta^5$ -desaturase in vivo (see Japanese Patent Application No. 63-53642; Japanese Unexamined Patent Publication KOKAI No. H1-243992).

### Example 2

According to the same procedure as described in Example 1, sesamin, curcumin (Wako Pure Chemical Industries, Japan) or piperonyl butoxide (Aldrich) was added in a reaction mixture at a concentration of 0.03 mg/ml. The result is shown in Table. 1.

Table 1

Test compound	Inhibition on $\Delta^5$ -desaturase	Inhibition on $\Delta^6$ -
	(%)	(%)
Sesamin	39.23	0
Curcumin	50.56	36.13
Piperonyl butoxide	32.47	0

### Example 3

First, 20 g of sesame oil was dissolved in 150 ml of acetone, and the solution was allowed to stand at -80°C overnight to precipitate an oil fraction. After filtration, the filtrate was evaporated in a rotary evaporator to remove the solvent, and an extract containing lignan compounds such as sesamin, which are  $\Delta^5$ -desaturase inhibitors, was obtained.

SD male rats 4 weeks old (102 g) were fed for 3 weeks. The feed contained 10% evening primrose oil (EPO) or safflower oil (SFO) as a fat source, and the above-prepared extract in an amount corresponding to 0 g, 10 g or 100 g of sesame oil (test groups were designated EPO-0, EPO-10 and EPO-100, as well as SFO-0, SFO-10 and SFO-100, respectively). After 3 weeks, the body weight, liver weight, plasma cholesterol, plasma triglyceride, plasma lipid,  $\Delta^5$ -desaturase activity and  $\Delta^6$ -desaturase activity in liver microsome,  $PGI_2$  production by the aorta, and an amount of  $TXA_2$  in plasma were measured. The desaturase activity was measured as described in Example 1, and other measurements were carried out according to conventional procedures. The results are shown in Tables 2 and 3.

Table 2

No.	Initial body weight	Final body weight	Increase	Increase/day	Total feeding taken	Feeding taken/day
	(g)	(g)	(g)	(g/day)	(g)	(g/day)
EPO-0	102 ± 3	270 ± 11	167 ± 10	8 ± 0	384 ± 18	18 ± 1
EPO-10	103 ± 3	265 ± 13	162 ± 11	8 ± 1	382 ± 13	18 ± 1
EPO-100	103 ± 2	265 ± 10	161 ± 8	8 ± 0	385 ± 13	18 ± 1
SFO-0	103 ± 2	269 ± 7	166 ± 6	8 ± 0	385 ± 8	18 ± 0
SFO-10	103 ± 2	276 ± 7	173 ± 6	8 ± 0	402 ± 14	19 ± 1
SFO-100	103 ± 2	269 ± 7	166 ± 5	8 ± 0	388 ± 9	18 ± 1
No.	Efficiency of feeding	Liver weight	Plasma CHOL	Plasma TG	Plasma PL	
		(g)	(mg/dl)	(mg/dl)	(mg/dl)	
EPO-0	0.43 ± 0.01	14.57 ± 0.01	109.4 ± 5.7	189.7 ± 15.8	251.8 ± 16.7	
EPO-10	0.42 ± 0.02	14.59 ± 0.83	101.9 ± 6.8	165.2 ± 11.6	239.0 ± 17.5	
EPO-100	0.42 ± 0.01	16.71 ± 0.94	75.1 ± 4.4	149.9 ± 24.9	216.3 ± 8.2	
SFO-0	0.43 ± 0.01	14.49 ± 0.61	89.4 ± 2.6	253.9 ± 29.2	267.7 ± 9.4	
SFO-10	0.43 ± 0.01	14.80 ± 0.78	83.4 ± 4.5	175.0 ± 18.9	238.3 ± 10.6	
SFO-100	0.43 ± 0.01	16.83 ± 0.72	74.8 ± 4.7	163.6 ± 14.1	222.3 ± 11.7	
CHOL: cholesterol TG: triglyceride PL: phospholipid						

Table 3

$\Delta^5$ - and $\Delta^6$ -desaturase activity in rat liver microsome						
(pmol/min/mg protein)	EPO			SFO		
	0	10	100	0	10	100
$\Delta^6$ -desaturase activity	42.1	35.0	59.41	34.1	34.2	61.71
$\Delta^5$ -desaturase activity	48.6	39.5	34.81	55.5	48.8	25.21

As seen from the above, the feeding of sesame oil extract for 3 weeks has no influence on the increase of body weight and liver weight, and therefore, does not influence the growth. Moreover, the  $\Delta^5$ -desaturase activity in microsome was reduced in rats which received the extract. Also, the feeding of the extract provided a tendency toward a lowering of cholesterol levels.

As described above, the present composition comprising  $\Delta^5$ -desaturase inhibitor can be used specifically to inhibit  $\Delta^5$ -desaturase occurring in animals, such that an in vivo level of dihomono- $\gamma$ -linolenic acid increases and prostaglandin 1 series compound is derived from dihomono- $\gamma$ -linolenic acid and a cascade thereof, resulting in an improvement of inflammation, thrombosis and hypertension conditions. Moreover, the present desaturase inhibitors did not effect  $PGI_2$  production by the aorta and an amount of  $TXA_2$  in plasma, showing that the present inhibitors do not influence the arachidonic acid cascade.

#### Claims

1. A composition for inhibiting  $\Delta^5$ -desaturase comprising an effective ingredient selected from the group consisting of fignan compounds, curcumin and piperonyl butoxide.

2. A composition according to claim 1 wherein the lignan compound is selected from the group consisting of sesamin, sesaminol, episesamin, episesaminol, sesamol, 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane, 2,6-bis-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane, and 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenoxy)-3,7-dioxabicyclo[3.3.0]octane.

3. A composition according to claim 1, wherein the effective ingredient is selected from the group consisting of an extract prepared by extracting sesame oil with an organic solvent and an extract prepared by extracting sesame seeds with an organic solvent.

4. Use of a lignan compound, curcumin or piperonyl butoxide in the preparation of a medicament for the inhibition of  $\Delta^5$ -desaturase.

5. Use of a lignan compound, curcumin or piperonyl butoxide in the preparation of a medicament for increasing in vivo levels of dihomog $\gamma$ -linolenic acid.

6. Use of a lignan compound, curcumin or piperonyl butoxide in the preparation of a medicament for the treatment of inflammation, thrombus or high blood pressure.

7. Sesamin, episesamin, sesaminol, curcumin or piperonyl butoxide for medical use.

Fig.1

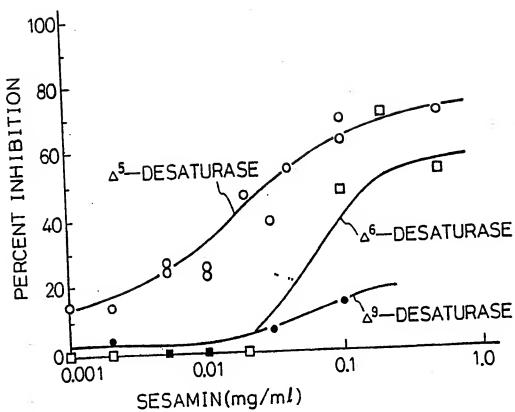




Fig.2

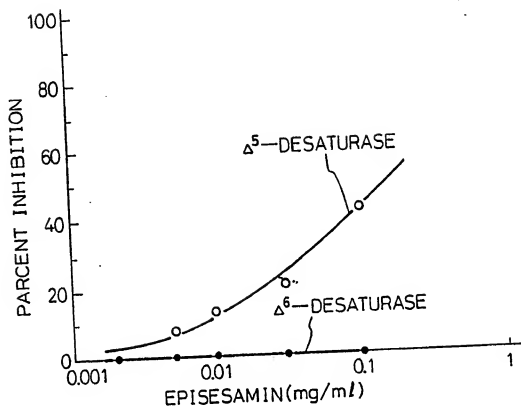


Fig.3

